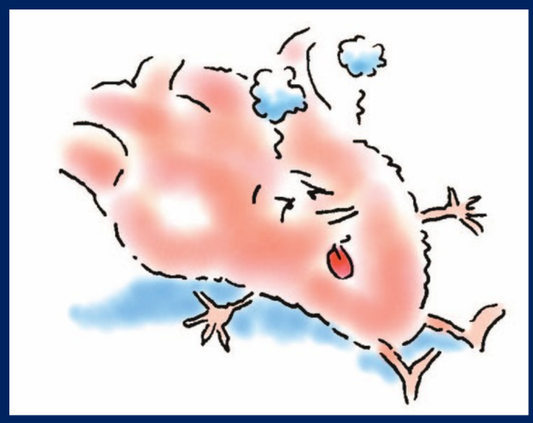
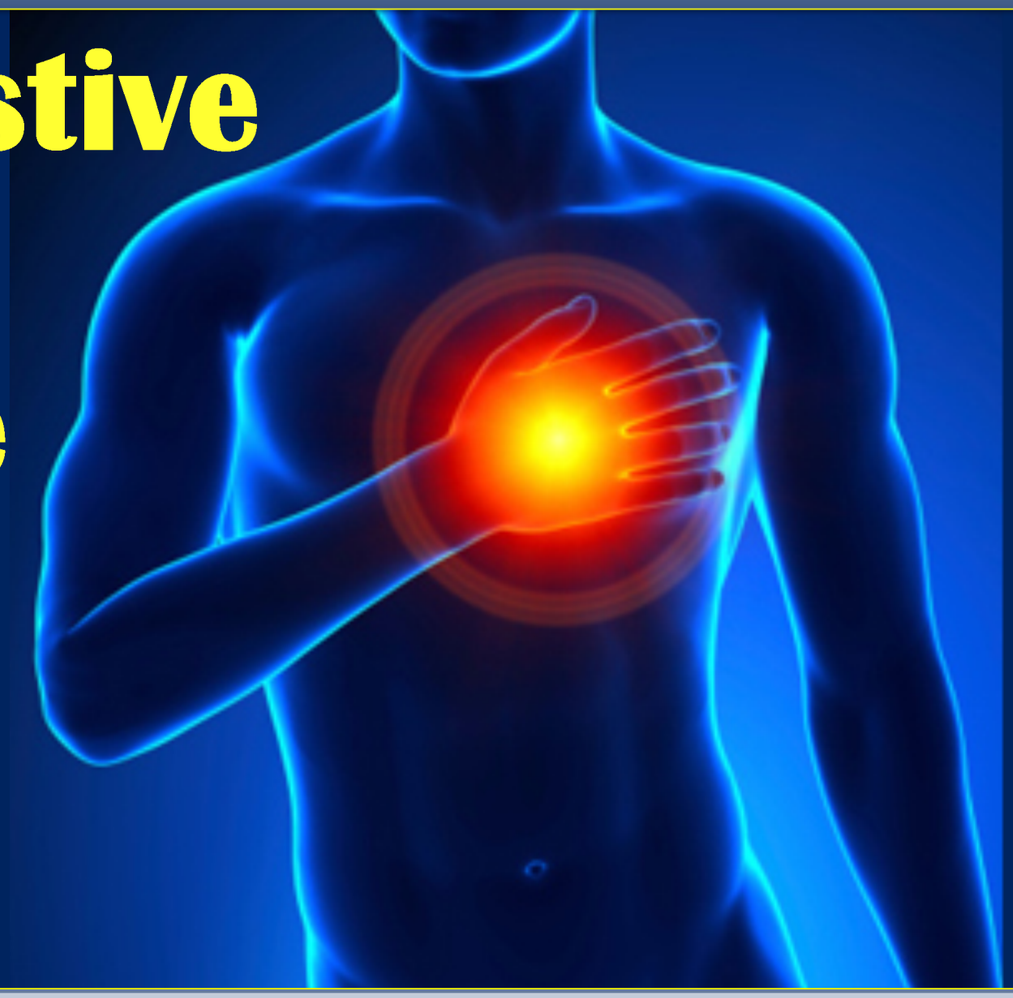
Draw Pharmacology in your mind



Congestive Heart Failure



If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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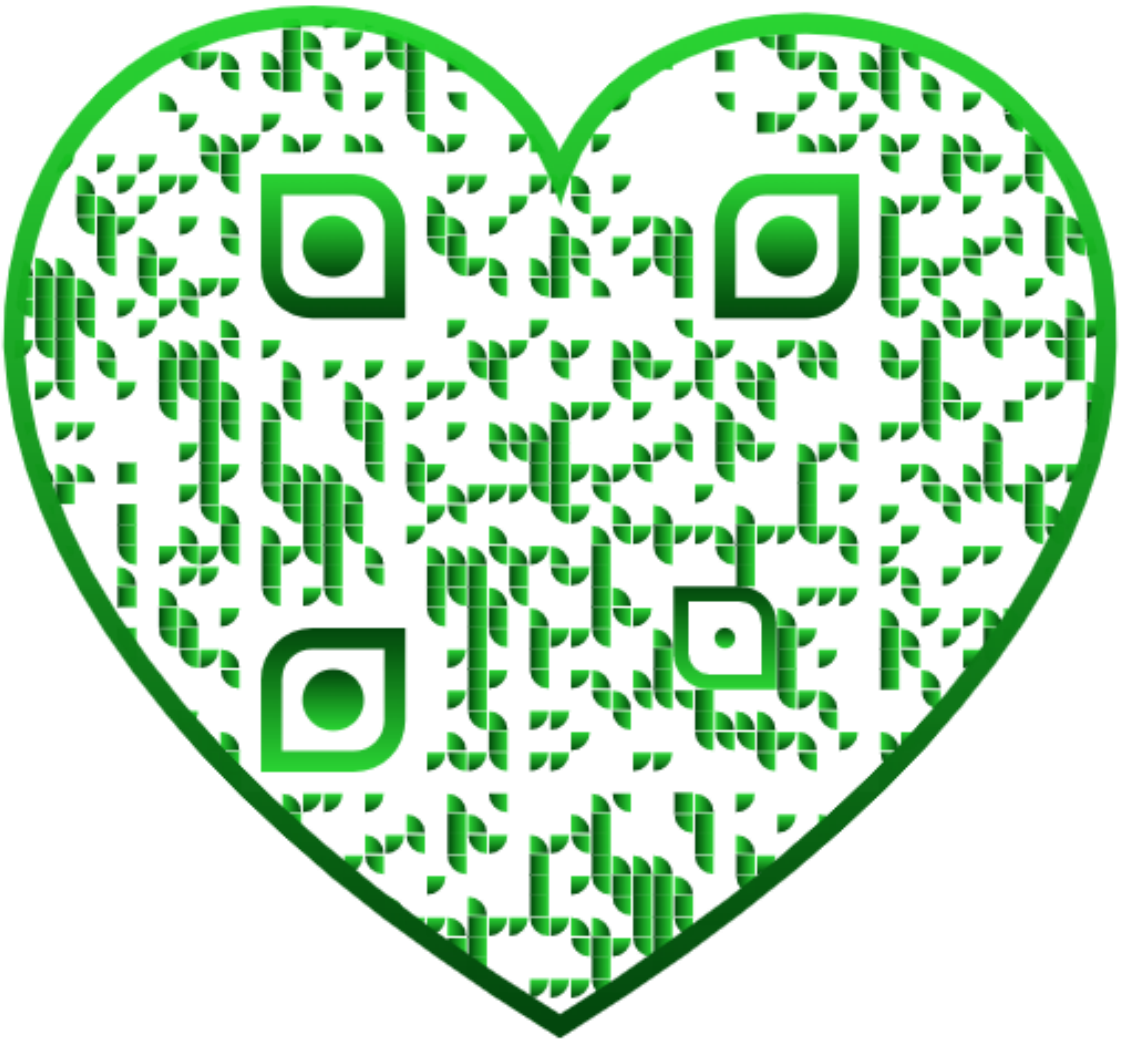
لا تنسونى من صالح دعائكم

Pharmacist. **Alaa Nasr**

د. آلاء نصر



CONGESTIVE HEART FAILURE

Force of contraction of the heart is **weaker** than normal → so, it can not pump all the blood reaching it → work capacity of the heart ⇓ → body can not get its blood demands **(heart fails !)**

Causes

1. **Anemia** *(the heart itself can not get the needed blood to work properly)*
2. **Disorder of the heart valves** *(so blood returns to the ventricles after pumping)*
3. **Congenital defect in the heart**
4. **Heart diseases**

ex.

1) Advanced coronary atherosclerosis → in this case coronaries *(which supply the heart with blood)* is blocked → so the heart can not get its needed blood to work

2) Cardiac arrhythmias → where heart beats more and more beats/min → so it can not pump all the blood in it

→ *And in both cases the heart finally fails*

What happens in CHF ? (mechanism ,signs and symptoms)

Lets take it step by step .. follow me

1. Force of contraction ⇓

→ so, Volume of blood pumped ⇓ *(stroke volume & cardiac output)* → so, **blood pressure ⇓** →

for this reason **compensatory mechanisms** are activated to ⇑ blood pressure which are:

a) Reflex tachycardia

b) Vasoconstriction → so arterial resistance in the kidneys ⇑ → Renal blood flow ⇓ → Glomerular filtration ⇓ → Retention of water and electrolytes in the body → **Edema**

Ok ?

2. Residual blood volume ⇑ *(blood that accumulates in the heart after each pump)*

→ so, Venticles dilate → leading to ⇑ **heart SIZE**

Think with me..

As the blood is accumulated in the ventricles, what happens to the blood entering the heart through vena cava ?

This leads to **congestion of vena cava** *(that why it is called **congestive heart failure**)*

Ph. Alaa Nasr

Cardiac glycosides (Digitalis)

- They have a **steroidal nucleus** containing an unsaturated lactone at C_{17} and one or more sugar residues at C_3
- **They are composed of:**

1. Aglycone part (non-sugar part) → for cardiotonic activity

2. Sugar part → for water solubility

1. Chemical nature

2. Effect on force of contraction

- **Digitalis glycosides ⇑ the force of contraction of the heart** → so the heart beats stronger → **ALL** the signs and symptoms are **reversed**
- *Is this action done by stimulating sympathetic nervous system !!*

→ **The answer is NO**

→ **The evidence** → Animals that are pre-treated with **Reserpine** *(depletes catecholamines stores)* or **Propranolol** *(β-blocker)* → still show **+ve inotropic effect** after administration of **digitalis**

Mechanism at cellular level

Lets take it step by step .. follow me

- There is a membrane-bound catalytic enzyme called **Na^+/K^+ ATPase enzyme that could be found activated/phosphorylated or deactivated/dephosphorylated** ***(keep in mind this is related to K^+)***

→ this enzyme hydrolyze ATP to produce energy → this energy is needed for Na^+ to get out of the cell in exchange with K^+

- **Ok?**
- Digitalis inhibit this enzyme when it is activated/phosphorylated so intracellular Na^+ concentration will ⇑ and K^+ ⇓
- Na^+ has to go out → so cardiac fibers possess **another mechanism** → which is exchange the intracellular Na^+ for extracellular Ca^{+2} → so the cardiac fibers will extrude Na^+ in exchange with Ca^{+2} without consuming energy **leading to:**

1. ⇑ intracellular Ca^{+2}

2. Inhibition of extrusion of Ca^{+2} outside the cells

3. Releasing Ca^{+2} stored in the sarcoplasmic reticulum

→ All this will ⇑ the concentration of Ca^{+2} intracellularly so myocardial contractility will ⇑ **(+ve inotropic effect)** *(Ca^{+2} interacts with the contractile proteins, actin and myosin)*

3. Effect on heart rate

Digitalis has -ve chronotropic effect = ⇓ heart rate = Bradycardia

Mechanism

1. Improvement of circulation (so no compensatory mechanisms)

2. Vagal mechanisms:

a) It stimulates **vagal nuclei in CNS** → so, ⇑ the vagal discharge at SAN (inhibitory) → so, ⇓ heart rate

b) ⇑ the sensitivity of SAN to the -ve chronotropic effect of **Ach**

c) Reflex sensitization of the **Carotid baroreceptors** *(to feel that the normal blood pressure as it is high → so ⇓ heart rate)*

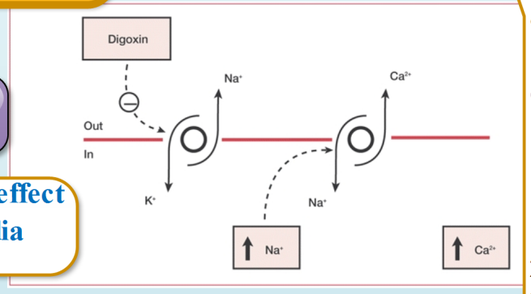
3. Extravagal mechanisms:

a) ⇓ the sensitively of SAN and AVN to the +ve chronotropic effect of **chatecholamines** (AD and NA), ⇓ the sympathetic stimulation

b) Partial AV block

Digitalis can ⇓ the speed of conduction through AV bundle *(conductivity through AV bundle ⇓)* → **ok, what is that mean ?** Digitalis can ⇑ the depolarization time → so, ⇑ the period when no impulse can spread *(this is called the **refractory period**)* → leading to ⇓ heart rate

***Take care** it is **partial** AV block not **complete** AV block as if it is complete it could lead to stop the heart completely !!*



Effect on K^+

- Digitalis binds to ATPase enzyme when it is activated / phosphorylated
- K^+ promotes its dephosphorylation

→ so, this ⇓ the affinity of the enzyme to bind to Digitalis

→ so, K^+ the ⇓ effect of Digitalis

– so, K^+ will be useful in case of **toxicity** and should be administered to **normal degitalized** patients (receiving Digitalis) to ⇓ the high intensity of Digitalis

Cardiac glycosides (Digitalis)

Ph. Alaa Nasr

Other choices for treatment

- **Amiodarone** New drug has a strong +ve inotropic effect
→ Its effect on stroke volume = Digitalis
→ Indicated for patients who have not responded to → Digitalis, vasodilators and diuretics
→ **Mechanism: Phosphodiesterase inhibitor** → ⇓ degradation of cAMP
• *cAMP mediates the excitatory effect of AD and NA on the heart*
→ so, ⇑ force of contraction

- **Correction of cause** (anemia, ischemia)
- **Vasodilators** → ⇑ coronary artery supply
a) ACE inhibitors → ex. Lisinopril (Zestril®)
b) Angiotensin antagonists → ex. Losartan
c) Nitrates & Nitrites
- **Sympathomimetics** ex. Dobutamine → ⇑ sympathetic influence to the heart
- **Diuretics** (get rid of edema, ⇓ blood volume, ⇓ venous return)

2. Cholestyramine (ion-exchange resin)

- It binds to **digoxin or digitoxin** in the GIT → ⇓ absorption
- **Solution:**
1. Avoid co-administration
2. Dose spacing

3. Hypokalemic agents

ex. Thiazide duiretics, Amphotricin B
- They ⇓ K^+ concentration in the body → so, ⇓ dephosphorylation of ATPase → Digitalis **toxicity**

8. Drug-Drug interactions

1. LME inducers

Antihistaminic, Anticonvulsant ..etc
- They ⇑ metabolism of **digitoxin** (plasma concentration ⇓) → underdigitalization
- **Solution:** the ⇑ **dose** of Digitoxin
- **Problem:** upon withdrawal of LME inducer → digitalis **toxicity**

4. Quinidine (Antiarrhythmic drug)

- **It interacts with Digitalis at 2 pharmacokinetic sites:**
1. Displacement of Digitalis from plasma protein binding site
2. ⇓ Renal clearance (excretion of **Digoxin**) → ⇑ the free concentration in the blood → ⇑ incidence of toxicity

Treatment

1. Stop digitalis therapy
2. ⇓ Ca^{+2} concentration by
- Stopping Ca^{+2} containing preparations
- Uning chelating agent
3. ⇑ K^+ concentration by
- Stopping hypokalemic preparation
- ⇑ K^+ (within limits) by administration of potassium syrup
4. Tachyarrhythmia ? use antiarrhythmic drug → ex. Propranolol, Lidocaine
5. Bradyarrhythmia ? use parasympatholytic drug → ex. Atropine
6. Cholestyramine, Cholestipol → ⇓ absorption of Digitoxin from GIT and half life by 50%
7. "Fab fragments" of Digoxin-specific antibody **Digibind** (IV)

Possible causes

1. Co-administration of diuretics depleting K^+
2. Low therapeutic index, so it is difficult to determine the end point for maximum therapeutic effect or for toxicity
3. The considerable variation in therapeutic dose from patient to another

6. Uses

1. Congestive heart failure
- **Its advisable to:**
a) ⇓ salt intake
b) Use diuretics except thiazide diuretics *(as they are hypokalemic)*
2. Different types of arrythmias
a) Atrial flutter
b) Atrial fibrillation
3. Paroxysmal tachycardia

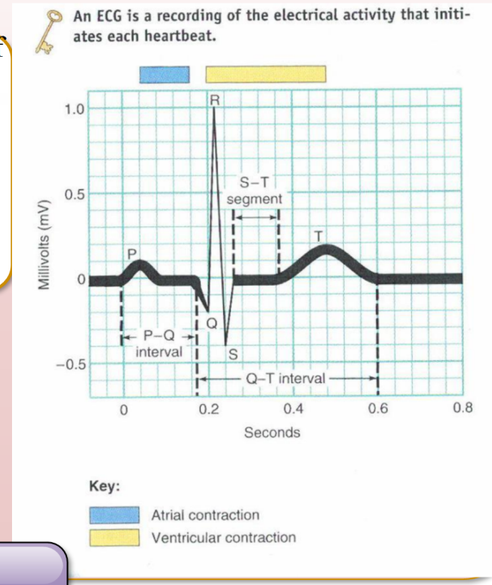
7. Toxicity

Signs & Symptoms

1. Tachyarrhythmia or bradyarrhythmia
2. Anorexia, nausea & vomitine *(as it stimulates CTZ),* abdominal pain
3. Neurotoxicity (peripheral neuritis)
4. Retinopathy = confused vision = seeing things green or yellow .. Very Very Very important .. so if a patient starts describing to a pharmacist that he sees everything in green for example, the pharmacist should refer him **IMMEDIATELY** to his physician

4. Effect on ECG

- PR interval represents the speed of conduction in AV bundle
- Digitalis causes **partial AV block**
→ ⇓ the conductance in AV bundle
(⇑ the refractory period)
→ so, we will have ECG with a **prolonged PR interval**



5. Kinetics

	Digitoxin	Digoxin	Ouabain
Absorption	- Lipophilic so, **completely** absorbed from GIT - Oral dose = IV dose	- Intermediate lipid solubility - **75-85%** is absorbed from GIT	- Water soluble so, only **5%** is absorbed from GIT - Used only IV
Distribution	- **90%** bound to plasma proteins - half life **7-9 days**	- **23%** bound to plasma proteins - half life **1.5-2 days (33-44 hrs)**	- **Not** bound to plasma proteins - half life **5 hrs**
Metabolism	Metabolized in **liver** to inactive metabolite	- Not metabolized in liver **so, preferred to patients with liver dysfunction**	
Excretion	Excreted in the bile **so, preferred to patients with renal dysfunction**	Excreted unchanged by **kidneys** in the urine	

At equilibrium the concentration at the cardiac muscle is **15-30** times more than in the plasma → **Preferential accumulation**

Doses

Digitoxin	Total initial dose	Maintenance dose
Orally IV	1-2 mg (24-48hrs) 1-1.5 mg (24 hrs)	0.1-0.2 mg

Digoxin	Total initial dose	Maintenance dose
Orally IV	1-3 mg 0.7-1 mg	0.5 mg

Ouabain -only IV
- 1 mg (2 hrs) divided every 15-30 min
- Used as initial dose only (initial digitalization)